

REMARKS

Claim Rejections - 35 USC § 112

Claim 34 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 34 was rejected because “the phrase ‘comprises less than 5 purine residues positively charged enhancer is an amine group’. It is not clear if the nucleic acid comprises less than 5 purine residues or if the positively charged enhancer comprises less than 5 purine residues.” Applicants respectfully traverse this rejection.

Claim 34 has been amended to recite “wherein the nucleic acid comprises less than 5 purine residues.” That is, “positively charged enhancer is an amine group” has been deleted from the claim. Applicant submits that amended claim 34 is clear and definite and respectfully requests withdrawal of the rejection.

Claim Rejections - 35 USC § 102

Claims 1-2, 5-7, 9-10, 13-17, 37-38, 42, 44-45 were rejected under 35 U.S.C. 102(e) as being anticipated by Mirkin et al. (US Patent Application Publication 2003/0211488A1 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com). Applicant respectfully traverses the rejection.

“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegall Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Independent claims 1 and 22 have been amended to recite, *inter alia*, “the positively charged Raman signal enhancer maintaining a positive charge capable of interacting with a negatively charged species after binding with the probe-target complex.” Independent claim 33 has been amended to recite, *inter alia*, “the

positively charged Raman signal enhancer maintains a positive charge capable of interacting with a negatively charged species after binding with the probe-target complex." Support for these amendments can be found in at least paragraphs [0021] and [0050] of the specification. No new matter has been added. These features are not taught by Mirkin.

In rejecting claims 1-2, 5-7, 9-10, 13-17, 37-38, 42, 44-45, the examiner makes several incorrect statements including:

- I. Mirkin et al. teaches that the oligonucleotide is attached to the phosphoramidite and the linker is attached to the DMT (displayed as MMTO on the figure) (p. 10 paragraph 158). Therefore the positively charged amine is not affected by the attachment of the linker and the oligonucleotide and would maintain its positive charge after binding to with the probe-target complex. The amine group on the Cy3 label is one "positively charged Raman signal enhancer" comprised in the Raman active probes. (page 5, lines 1-6)
- II. The declaration asserts that the charge of Cy3 label is lost when the probe of Cao et al. is further bound to a gold nanoparticle. Applicant is referring to the positive charge of the Cy3 label, while the examiner is designating the positively charged amine group located on the Cy3 as the enhancer. (page 9, lines 10-13)
- III. The Cy3 dye as maintains a positive charge of the N group based upon the fact that the N group is not involved in the attachment of the Cy3 molecule either to the probe or to the nanoparticle. The declaration has not discuss or pointed to the structure of the Cy3 molecule to show how the positive charge of the N group is removed based upon binding to the nanoparticle. (page 9, line 21 to page 10, line 3)
- IV. The reply asserts that the claimed nucleic acid tag complex is not attached to a metal particle. However, the claims are not limited to nucleic acids that do not have metal particles and would encompass any nucleic acid with a positively charged Raman signal enhancer. Further the figure provided by the declaration indicates the complex is attached to Ag metal particles. The "claimed invention" figure discloses limitations

which are not required by the claim, such as the Ag particles, the tag, and the positive amine group (for Claim 1). (page 10, lines 4-10).

Regarding statements I - III above, it is well known that gold nanoparticles are negatively charged (have a negative zeta potential). (See the attached articles: Burns et al "Solution ionic strength effect on gold nanoparticle..."; Lee et al "Amine-functionalized gold nanoparticles..."; Lung et al "Preparation of Gold Nanoparticles..."). It is also well known that when a positively charged molecule contacts a gold particle, the molecule would be adsorbed to the negatively charged gold surface through electric static interaction and thus effectively loses its positive charge property even though the positively charged group remains. That is, when Cy3 loses its charge on gold particle surface, Cy3 can no longer act as a free positive ion accessible to interact with other negatively charge species. A positive dye will not be attracted to the gold surface if the gold surface is pre-coated with other positively charged compounds and changes its zeta potential to positive before contacting with the dye. This was not the case in Cao. Nor is this the case in Mirkin. Mirkin, like Cao, teaches a Raman probe produced by attaching Cy3 labeled oligonucleotide strands to gold nanoparticles (silver coated). (Abstract and paragraphs [0144]-[0146]).

Regarding statement IV, as clearly stated in the abstract of Cao's paper, it is the gold particle surface that promotes the deposition of silver, not the dye. In the presently claimed invention, however, it is the freely available positively charged group that promotes aggregation of silver particles. Further there is a difference in mechanism for silver aggregation formation. In Cao, silver nanoparticles were formed directly on gold by reduction of silver ions. In the instant application, silver nanoparticles are pre-formed as a reagent and are attracted to the positively charge enhancer to form larger aggregate. That is, contrary to the assertions of the Examiner, the silver particles illustrated in the Su declaration are not attached to the complex, they are clustered about it. Further, the Examiner's statement that "the claims are not limited to nucleic acids that do not have metal particles and would encompass any nucleic acid with a positively charged Raman signal enhancer" is also incorrect. As discussed in the Su

declaration, attaching the nucleic acid having a positive charge to a gold particle would remove the positive charge from the nucleic acid. Amended independent claims 1, 22, and 33, however, recite "the positively charged Raman signal enhancer maintaining a positive charge capable of interacting with a negatively charged species after binding with the probe-target complex" or "the positively charged Raman signal enhancer maintains a positive charge capable of interacting with a negatively charged species after binding with the probe-target complex." A nucleic acid attached to gold particles simply would not meet this limitation.

Applicant respectfully requests withdrawal of the rejection.

Claim Rejections - 35 USC § 103

Claim 3-4 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al. (US Patent Application Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com) in view of Mirkin et al. (US Patent 6361944 March 26, 2002) (referred to as Mirkin B). Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al. (US Patent Application Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com) in view of Pastinen et al. (Genome Research July 2000 Vol. 10(7) p. 1031). Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al. (US Patent Application Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com) in view of Lane et al. (US Patent 5,770,365 June 23, 1998). Claims 22-24, 26-27, 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al. (US Patent Application Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com) in view of Chan et al. (US Patent Application Publication March 27, 2003) and Corbierre et al. (Journal of American Chem. Soc 2001 Vol. 123 p. 10411). Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al. (US

Patent Application Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com) in view of Chan et al. (US Patent Application Publication March 27, 2003) and Corbierre et al. (Journal of American Chem. Soc 2001 Vol. 123 p. 10411) as applied to claims 22-24, 26-27, and 29-32 above and further in view of Bruchez, Jr. et al. (US Patent Application 09/815585 March 21, 2002). Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al. (US Patent Application Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com) in view of Chan et al. (US Patent Application Publication March 27, 2003) and Corbierre et al. (Journal of American Chem. Soc 2001 Vol. 123 p. 10411) as applied to claims 22-24, 26-27, and 29-32 above and further in view of Livak et al (US Patent 5723591 March 3, 1998). Claims 33-34 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al. (US Patent Application Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com) in view of Alivisatos et al. (US Patent 6884478 April 26, 2005). Claims 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al. (US Patent Application Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com) in view of Alivisatos et al. (US Patent 6884478 April 26, 2005) as applied to Claims 33-34 and in view of Mirkin et al. (US Patent 6361944 March 26, 2002) (referred to as Mirkin B). Applicant respectfully requests withdrawal of the rejections.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). *See also* MPEP 2143.03. Further, "Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness". *KSR Int'l Co. v. Teleflex Inc.*, No. 04-1350, slip op. at 11 (U.S. April 30, 2007)(citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

As discussed above, independent claims 1 and 22 have been amended to recite, *inter alia*, "the positively charged Raman signal enhancer maintaining a positive charge capable of interacting with a negatively charged species after binding with the probe-target complex." Independent claim 33 has been amended to recite, *inter alia*, "the positively charged Raman signal enhancer maintains a positive charge capable of interacting with a negatively charged species after binding with the probe-target complex." These features are neither taught nor suggested by the applied references. Indeed, the Examiner has failed to provide even a rational basis as to why one of ordinary skill in the art at the time of the invention would have modified the invention of Mirkin to yield a method in which "the positively charged Raman signal enhancer maintaining a positive charge capable of interacting with a negatively charged species after binding with the probe-target complex" as recited in amended independent claims 1 and 22 and "the positively charged Raman signal enhancer maintains a positive charge capable of interacting with a negatively charged species after binding with the probe-target complex" as recited in amended Independent claim 33.

Double Patenting

Claims 1-17, 22-34, 36-38, 41-45 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-4 of copending Application No. 11414611.

Because the claims of both applications may be amended significantly during prosecution, Applicant respectfully requests this rejection be held in abeyance until the indication of allowable subject matter.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicant request a one-month extension of time and submits related fee in the attached Petition. The Director is also authorized to charge any additional fees necessary and/or credit any overpayments to Deposit Account No. 03-3975, referencing Docket No. 043395-0377929.

Respectfully submitted,

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- ATTACHMENTS